

Tuberculosis

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TB in a Nutshell

- **Chronic granulomatous infection caused by the *Mycobacterium tuberculosis* complex**
 - *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti*
- **Spread by aerosolized infectious droplets from patients with active pulmonary TB**
- **Lung disease is the most common manifestation**
 - all organs can be involved
- ***M. bovis* is a significant cause of human disease where milk is not routinely pasteurized**

Tuberculosis - Global Impact

- Approximately 1/3 of the world is infected with TB
 - Someone is newly infected every second
- Single leading cause of death from an infectious agent
 - 7% of all deaths and 26% of all preventable deaths
 - 2 million deaths in 2001
- 8.5 million new cases

Salder, J infect Dis 1994; 169:1189-96

WHO. Global Tuberculosis Control. WHO Report 2000

Tuberculosis - Global Impact

- 95% TB cases and 98% deaths occur in developing countries
- Highest rates worldwide:
 - Andean region of South America
 - Haiti
 - “Upper Asia” - Afghanistan, Nepal, Indochina, Indonesia, and the Philippines
- Areas with the worst TB rates also have some of the highest rates of HIV seroconversion.

Tuberculosis

Disease caused by the “tubercle bacillus”

Complex of four subspecies of

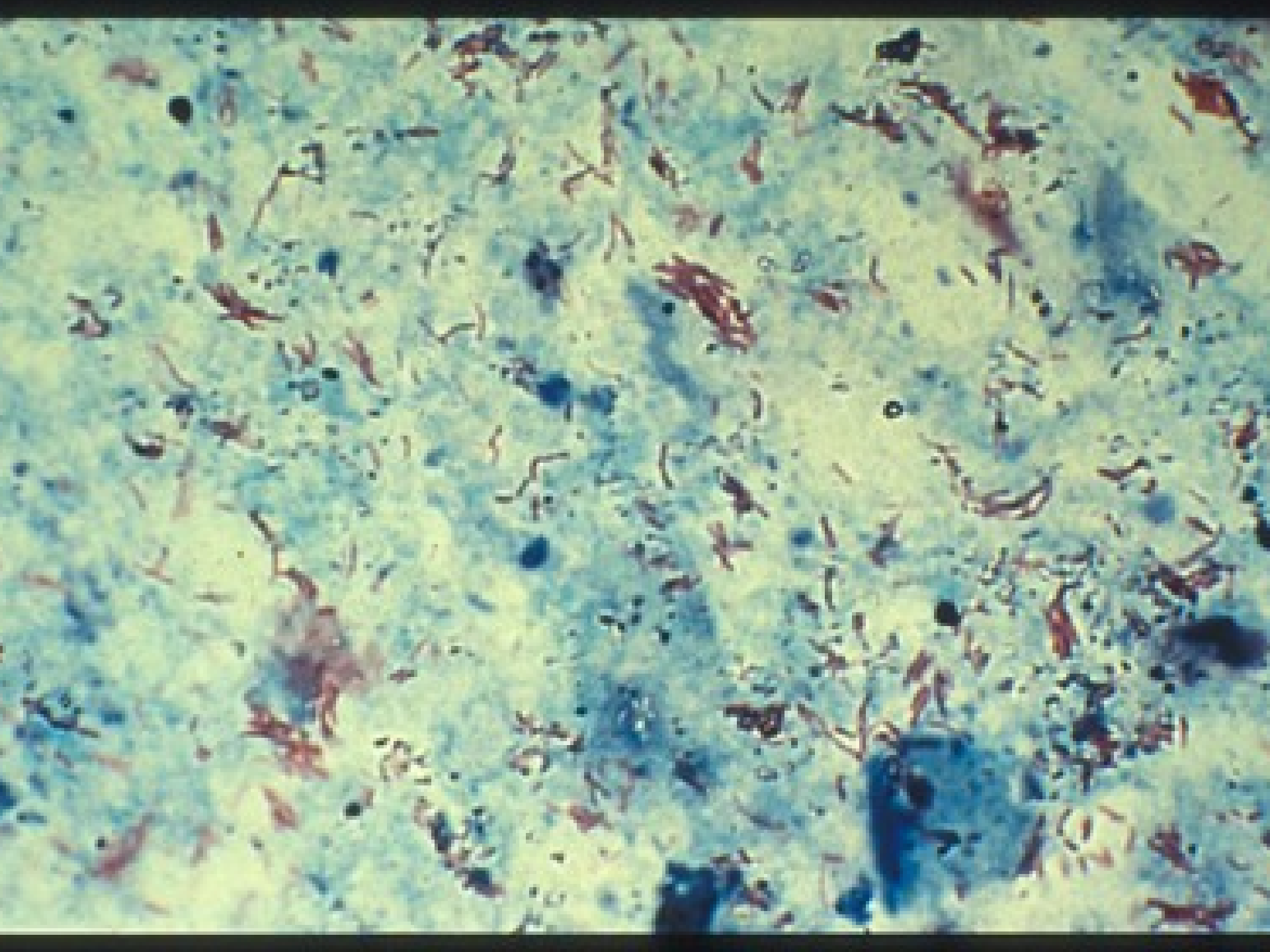
Mycobacteriaceae

- ***Mycobacterium tuberculosis***
 - Cause of the vast majority of worldwide TB infections
- ***M. africanum***
 - Rare cause of TB in Africa
 - Intermediate form between *M. tb* and *M. bovis*
- ***M. bovis***
 - Cattle were frequently infected
 - Milkborne transmission was common
 - Rare in developed countries
- ***M. microti***

Mycobacterium tuberculosis

Microbiology

- Order: Actinomycetales
- Family: Mycobacteriaceae
- Non-motile, non-spore forming, **obligate aerobe**
- Cell wall with high lipid % → **acid fast staining**
- Slow generation time: 15-20 hours



Tuberculosis - Transmission

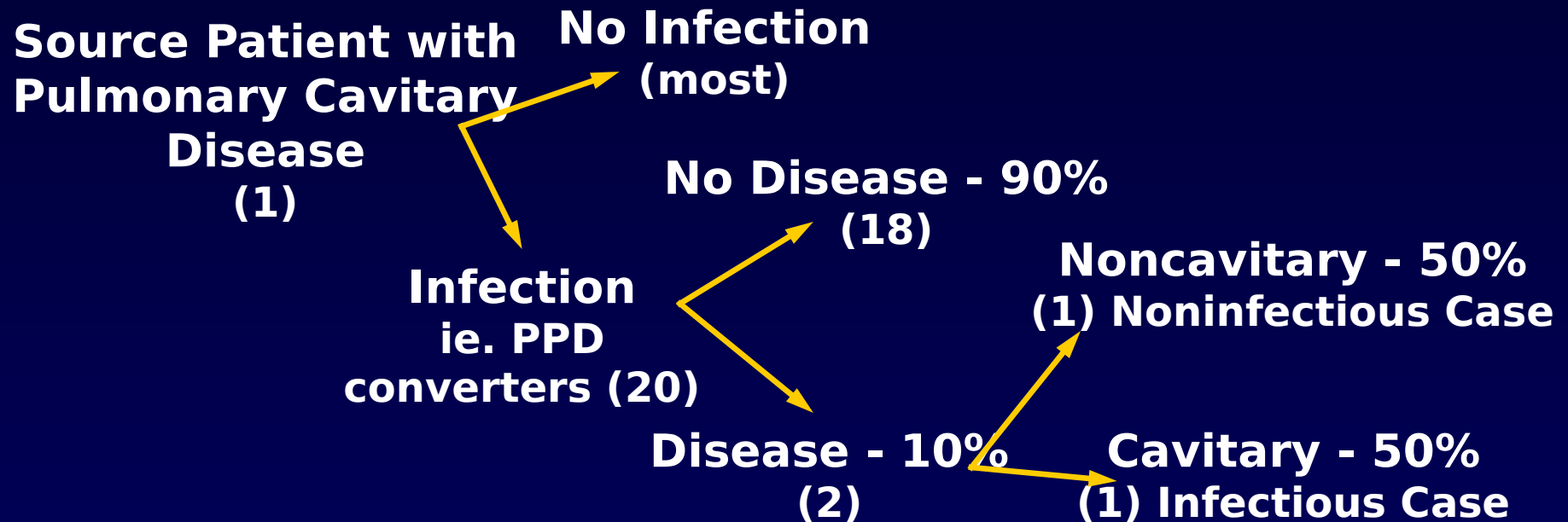
- **Most persons exposed to an active case do **not** become infected**
- **Persons with TB infection but no disease are **not** contagious**
- **Spread by airborne droplets, “droplet nuclei”**
- **Close contacts are at high risk of becoming infected**
- **10% of infected persons will develop clinical TB**

Infectiousness

- **Coughing**
- **Cough-inducing or aerosol-generating procedures**
- **Sputum smear positive for acid fast bacilli and:**
 - **Not receiving therapy**
 - **Just started therapy**
- **Cavitary lung lesions**
- **Poor clinical response to therapy**

Tuberculosis

Natural History of New Infection



An infectious patient (ie with pulmonary disease) needs to infect (cause PPD conversion) 20 contacts to maintain the same rate of infection in a population.

Tuberculosis - Natural History

If TB infected:

- **Normal Host**

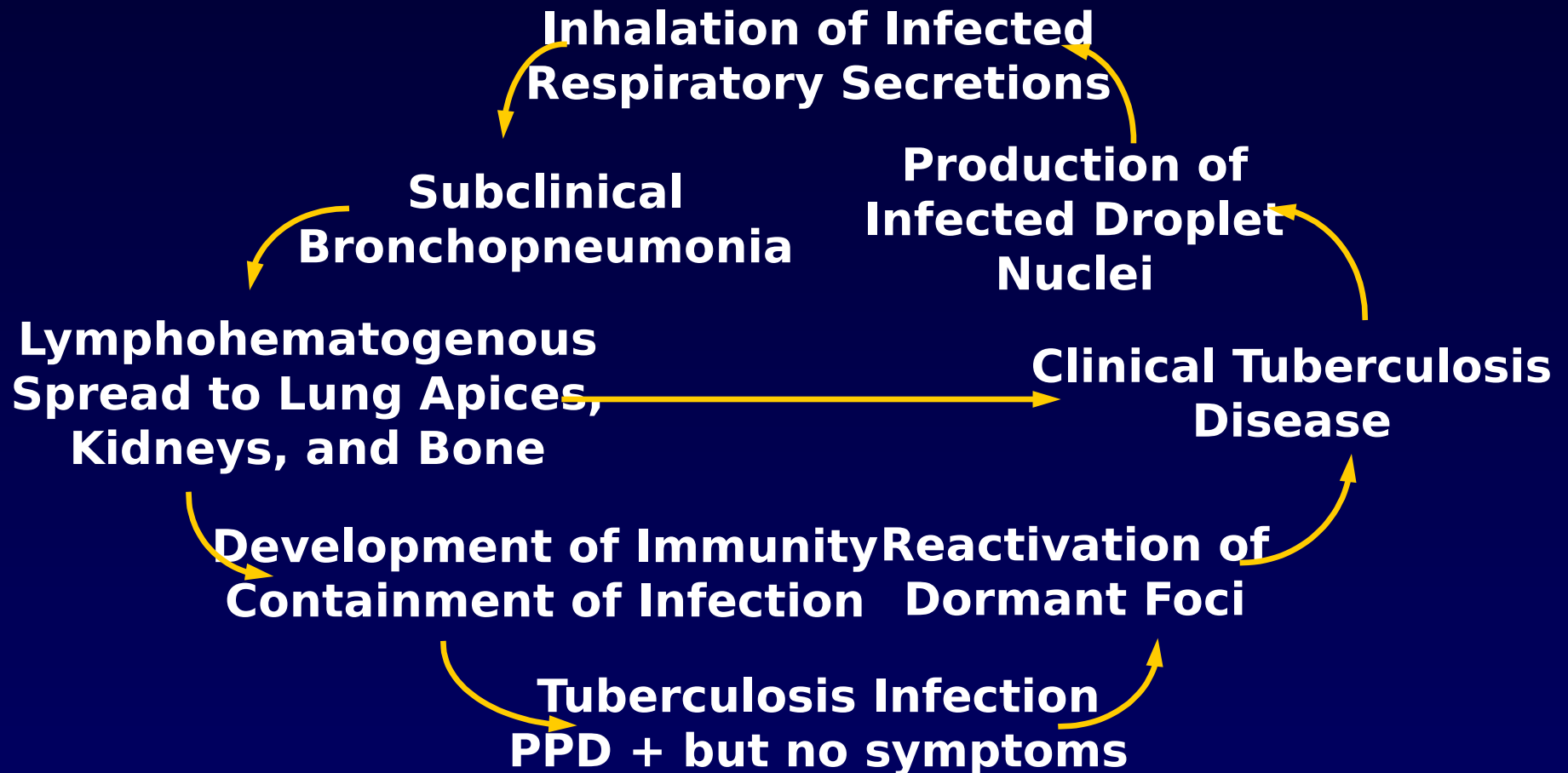
**5% risk of disease in first 2 years
+ 5% risk of disease throughout life**

10% overall risk of active disease

- **HIV positive**

5-10% risk/yr of active disease

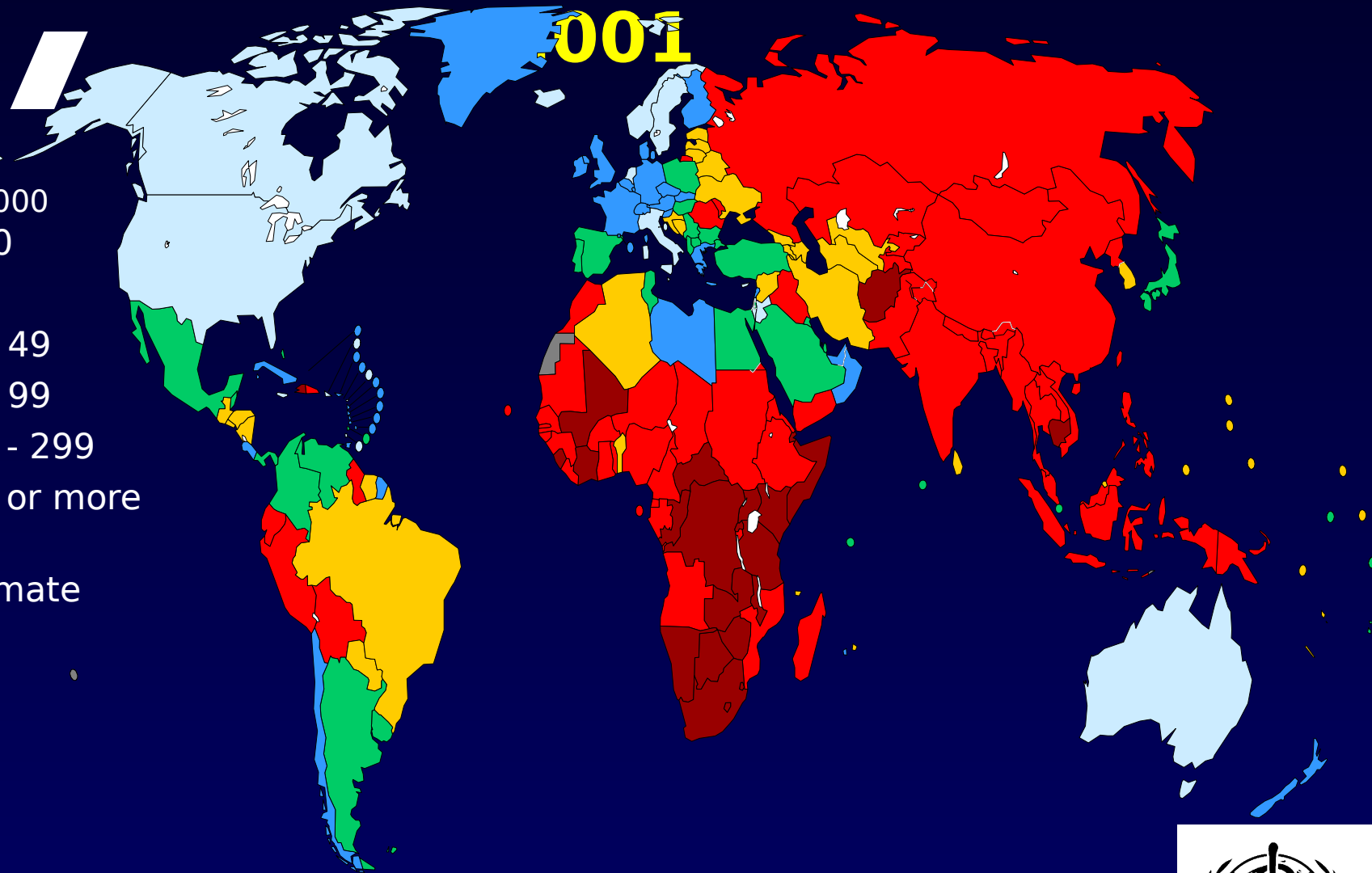
Tuberculosis - Pathogenesis



Tuberculosis - Organ Involvement

- **Lungs**
- **Pleura**
- **Central Nervous System**
- **Lymphatic System**
- **Genitourinary System**
- **Bones and Joints**
- **Any Other Body Organ or
Tissue**

Estimated TB Incidence Rates, 2001

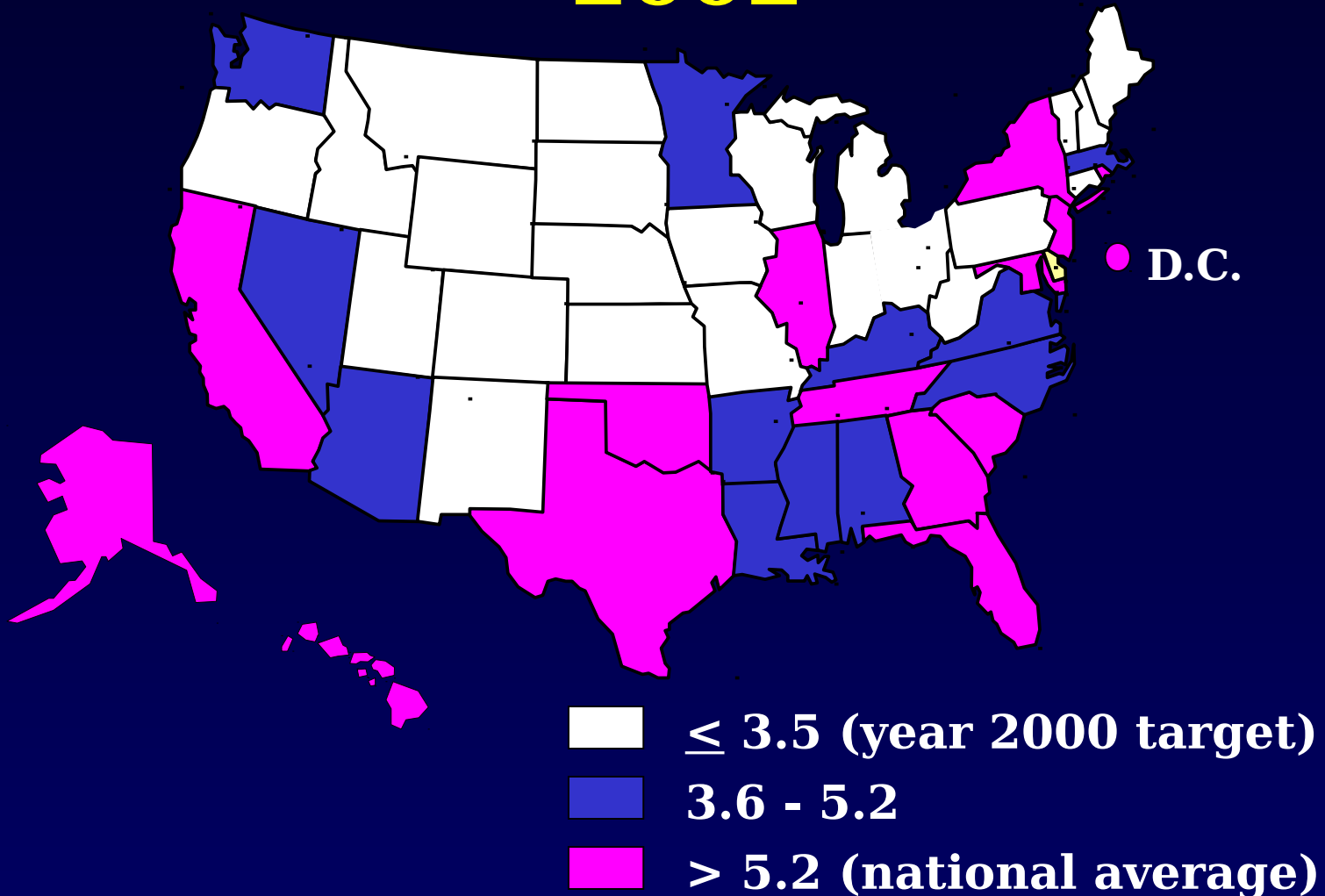


The designations employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. White lines on maps represent approximate border lines for which there may not yet be full agreement.

Reported TB Cases United States, 1981-2002

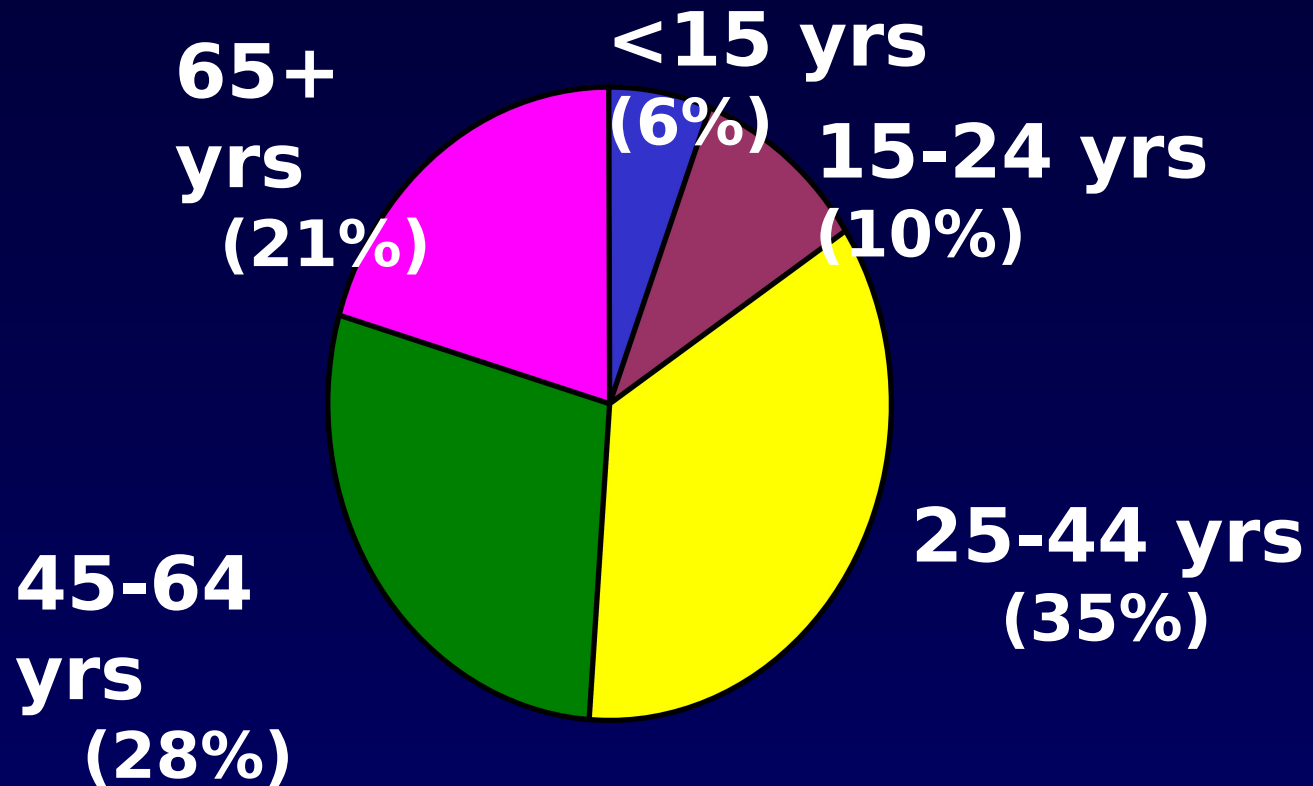


TB Case Rates, United States, 2002



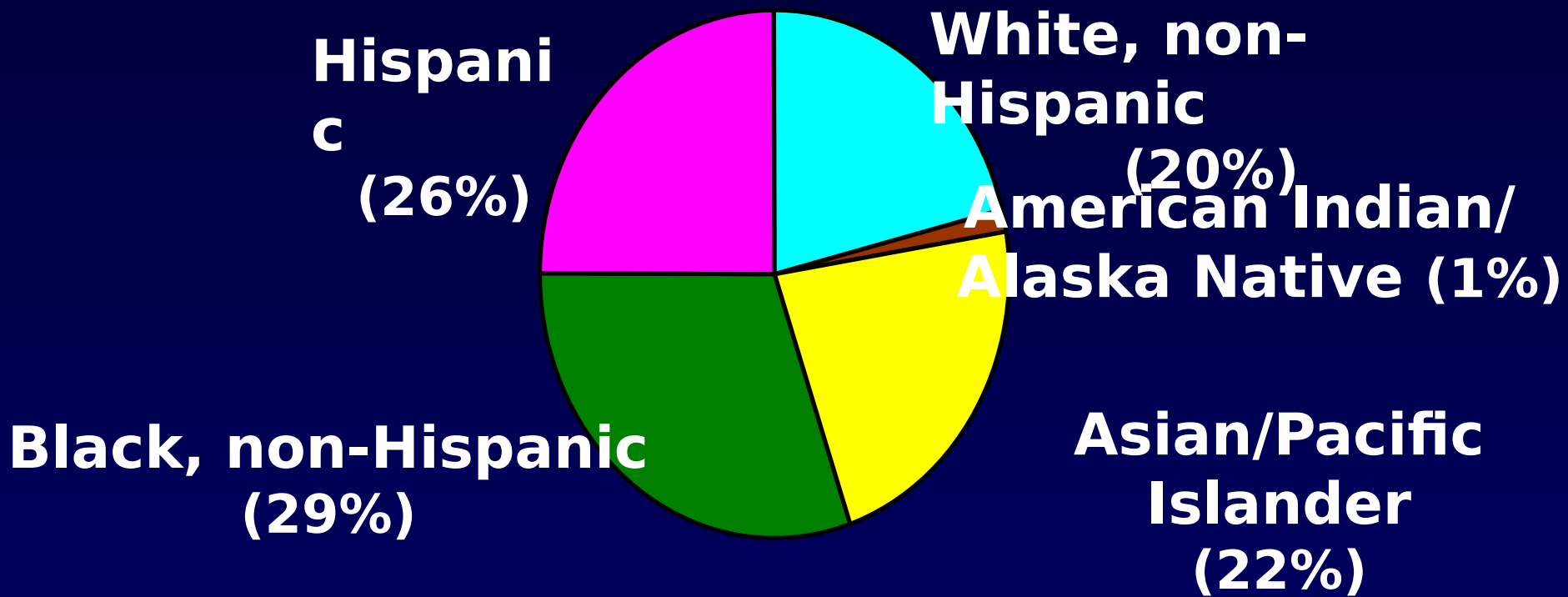
Rate: cases per 100,000

Reported TB Cases by Age Group United States, 2002



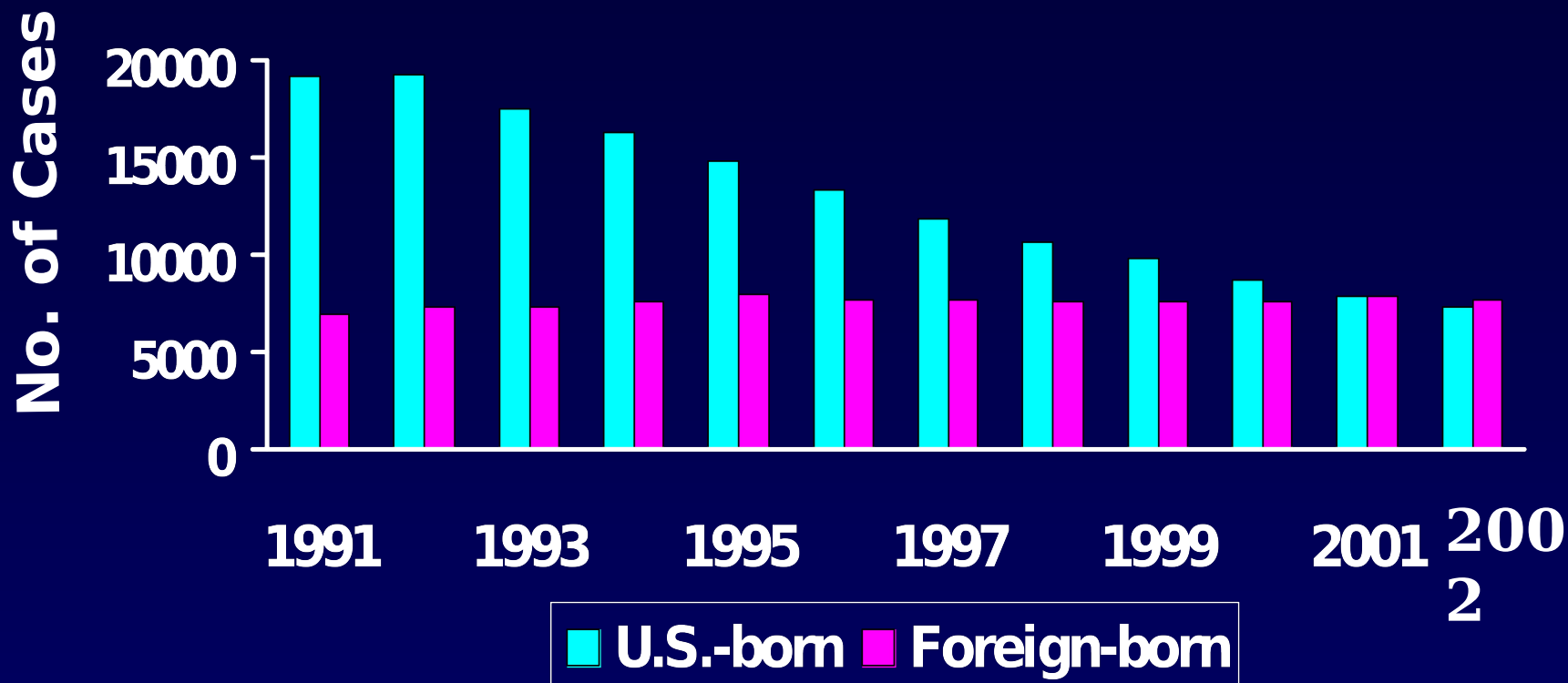
CDC. Reported TB in the US, 2002. Atlanta, GA: U.S. dept HHS, CDC 2003.

Reported TB Cases by Race/Ethnicity United States, 2002

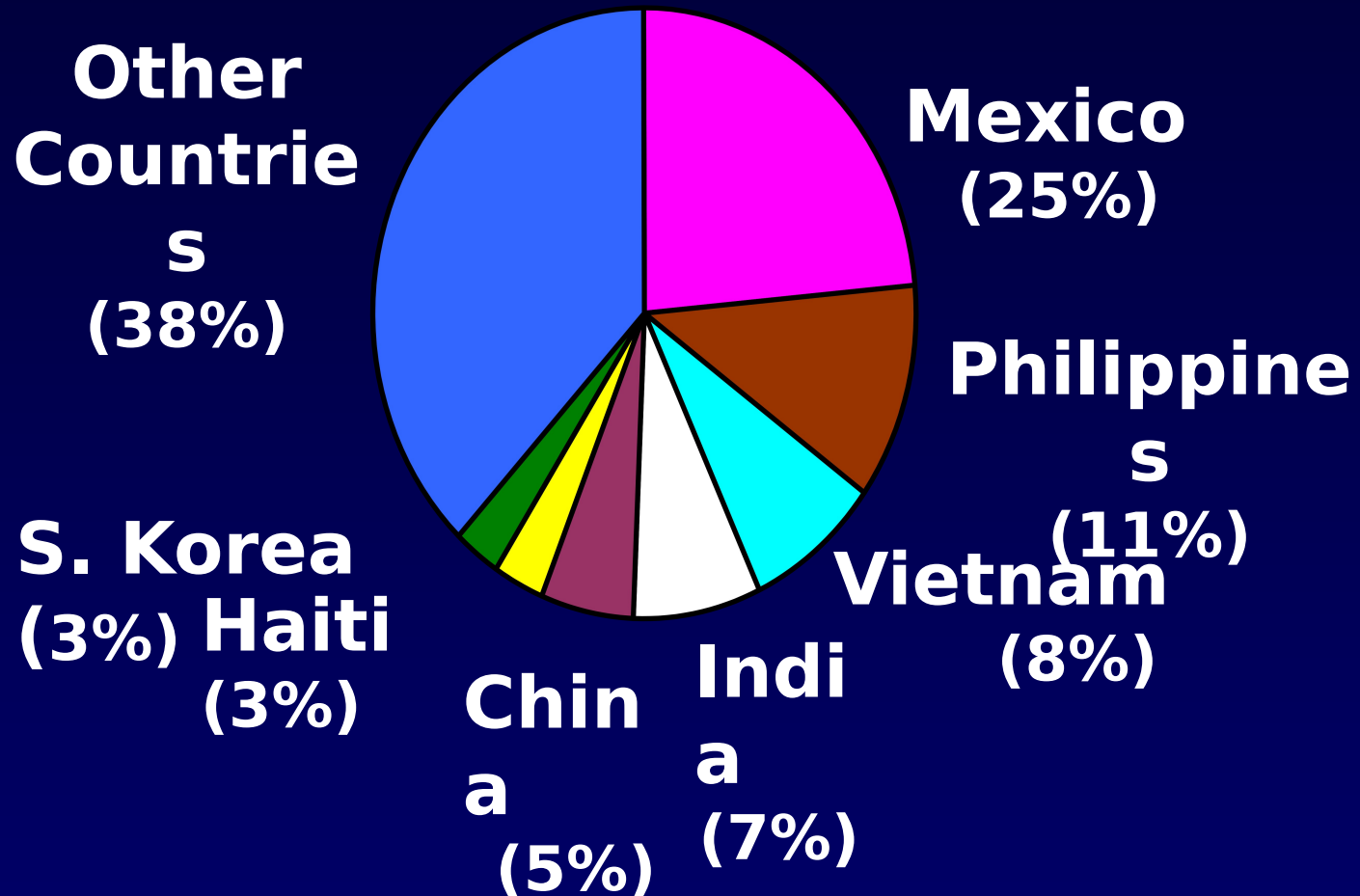


CDC. Reported TB in the US, 2002. Atlanta, GA: U.S. dept HHS, CDC 2003.

Number of TB Cases in U.S.-born vs. Foreign-born Persons United States, 1991-2002



Countries of Birth for Foreign-born Persons Reported with TB United States, 2002



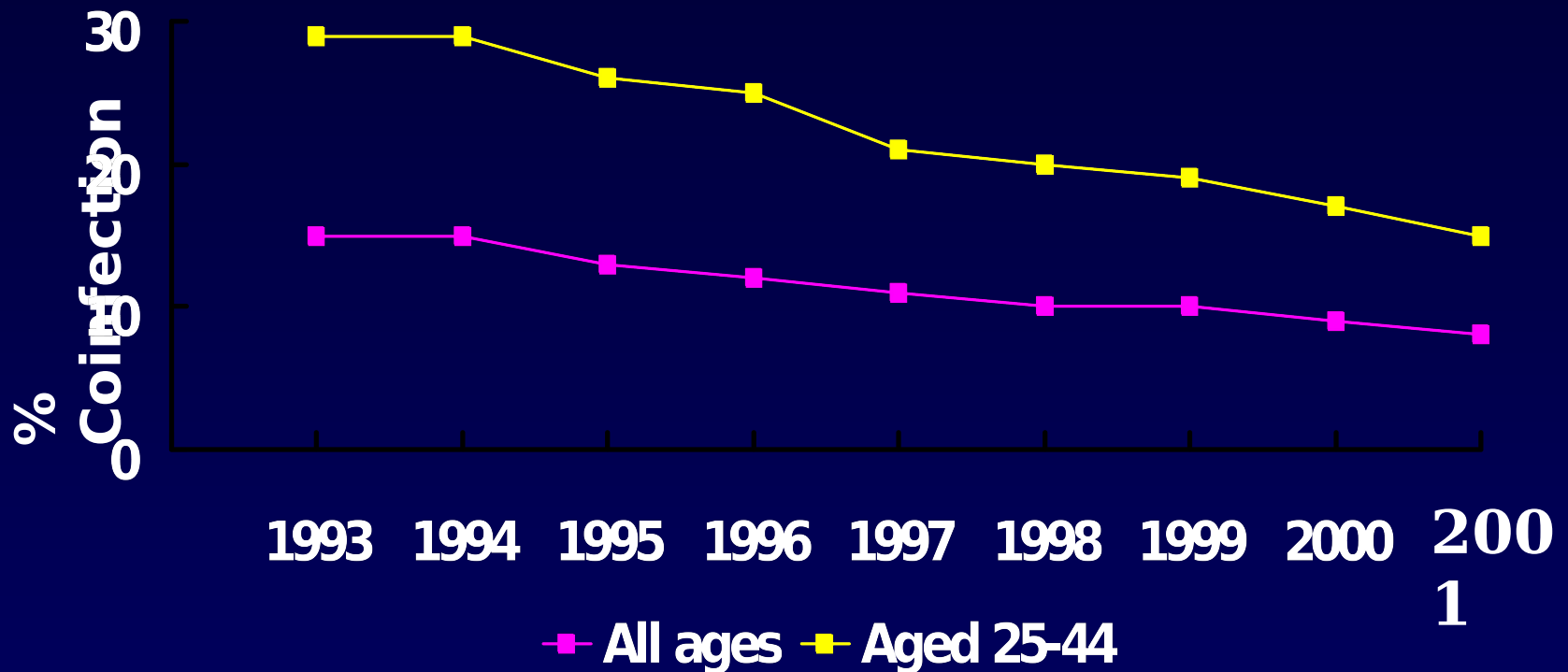
Tuberculosis - HIV Coinfection

- Much higher risk of developing TB disease
- Leading cause of AIDS-related deaths worldwide
 - 1/3 of all Aids-related deaths due to TB
- TB accelerates the course of HIV disease
 - Increased HIV RNA
 - Increased opportunistic infections
 - Increased mortality

Tuberculosis - HIV Coinfection

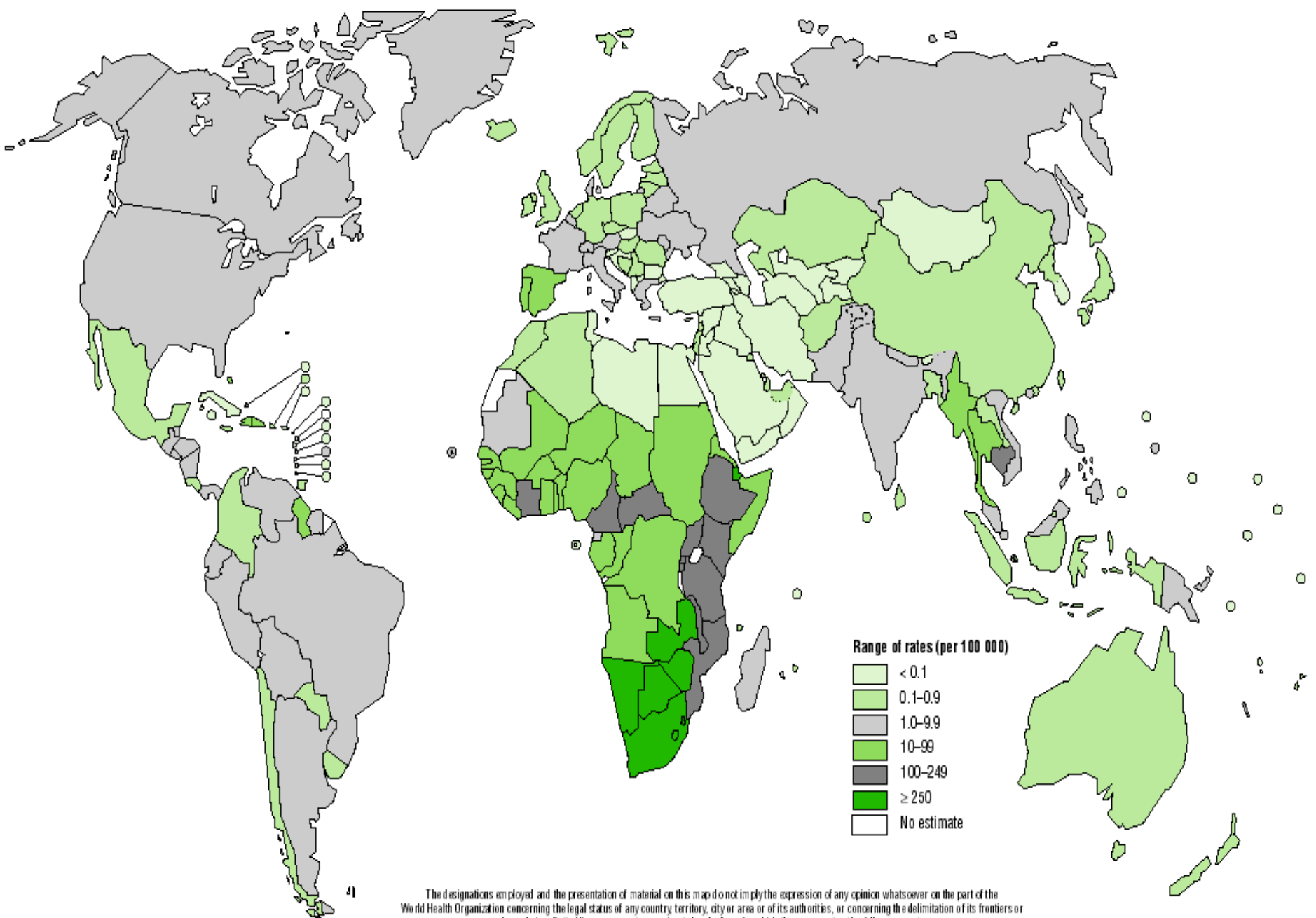
- **Fewer AFB positive smears (45% vs. 67%)**
- **+ Sputum cultures are comparable to non-HIV**
- **26-42% w/ AIDS-TB have + blood cultures for TB**

Estimated HIV Coinfection in Persons Reported with TB, United States, 1993-2001



Note: Minimum estimates based on reported HIV-positive status among all TB cases in the age group.

2. Estimated incidence rates of HIV-positive TB, 1999



Tuberculosis - Diagnosis

- History
- Physical
- Tuberculin skin test
- CXR
- Histology/Bacteriology
- Smear and Culture

A POSITIVE CULTURE IS
ESSENTIAL
TO CONFIRM DIAGNOSIS.

Pulmonary TB - Symptoms

- **Chronic cough**
- **Hemoptysis**
- **Fever/Chills**
- **Night sweats**
- **Fatigue**
- **Anorexia**
- **Weight Loss**

Frequency of symptoms in 142 adults and 76 elderly subjects with TB

Symptoms	Adults, N (%)	Elderly, N (%)	p value
Cough	77 (57)	31 (45)	0.113
Hemoptysis	25 (18.5)	4 (6)	0.025
Weight Loss	62 (45.9)	24 (35)	0.169
Fever	49 (36.3)	15 (22)	0.05
Anorexia	24 (17.8)	13 (19)	0.852
Night Sweats	45 (33.3)	9 (13)	0.003
Chest Pain	33 (24.4)	10 (15)	0.13
Dyspnea	29 (21.5)	16 (23)	1.92
Nonrespiratory	44 (32.6)	23 (33)	0.97
Chills	19 (14.1)	8 (12)	0.782
Asymptomatic	7 (4.9)	7 (9.2)	0.348

Pulmonary TB - Nonspecific Lab Abnormalities

- Anemia
- Elevated ESR
- Low albumin
- Hyponatremia
- Abnormal LAEs
- Leukocytosis
- Hypercalcemia

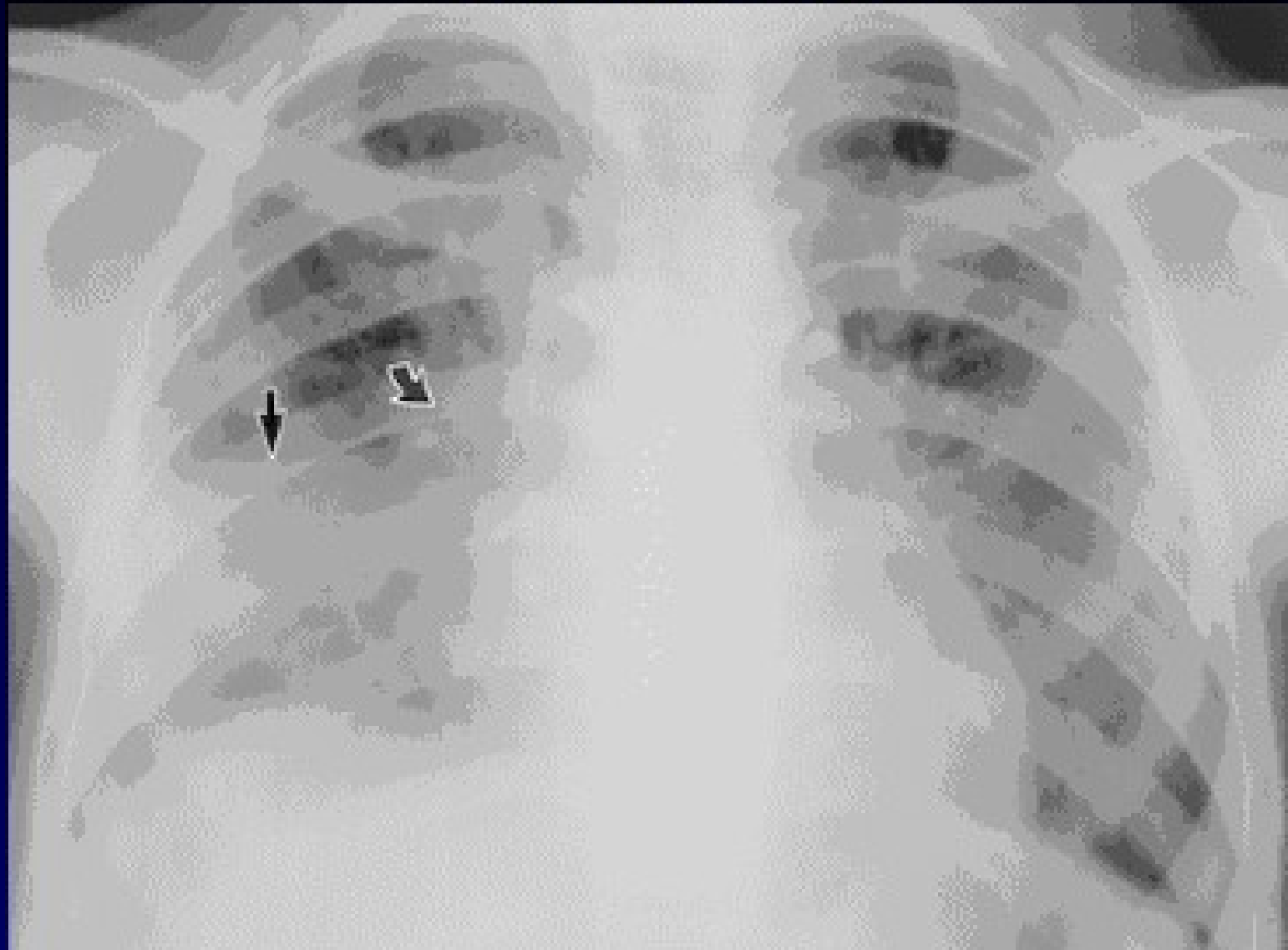
Extrapulmonary TB Disease

- Symptoms referable to the site involved
- 15% of new cases present with extrapulmonary dz
 - Much more common in HIV infected (up to 30%)
- Diagnosis can be complicated
 - 15-20% of cases have a negative PPD.
 - 85% have a normal chest x-ray.

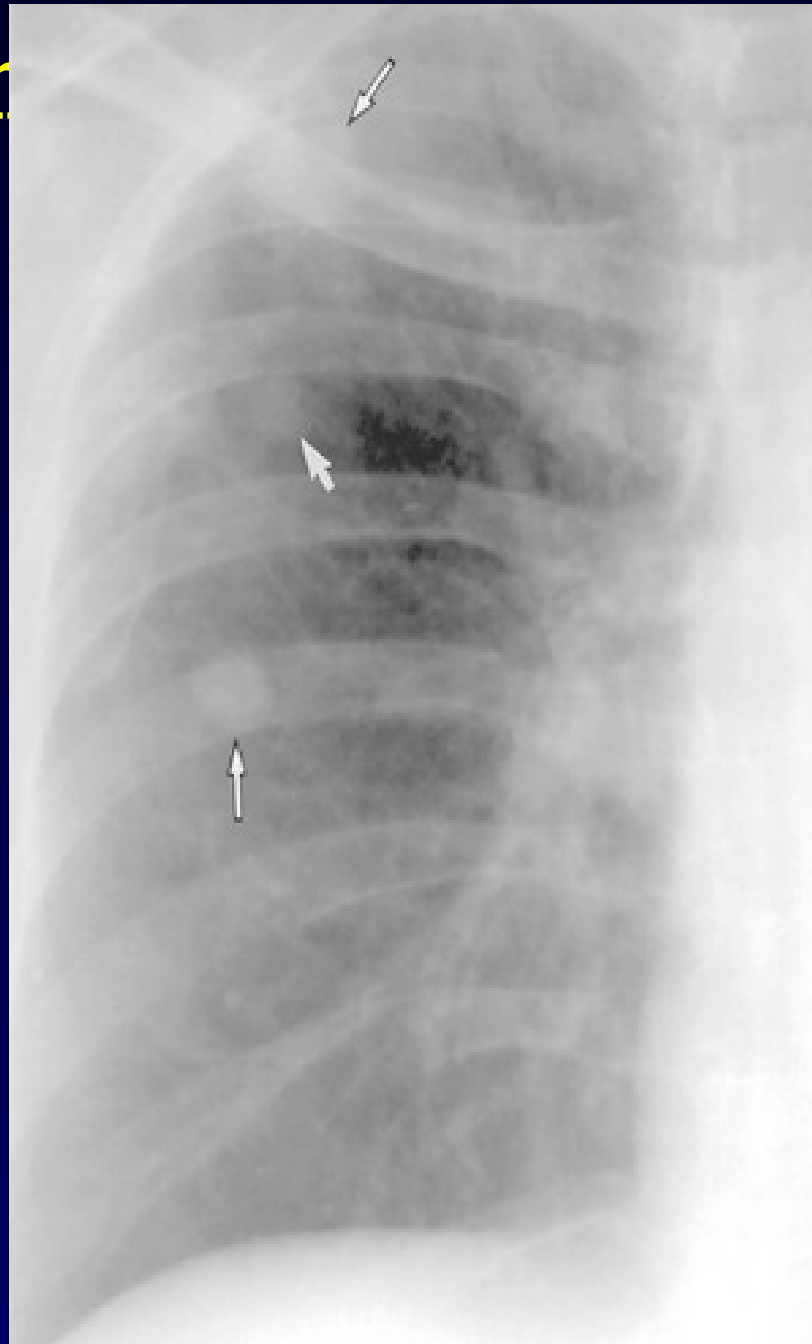
Tuberculosis - Miliary Disease

- **Blood-borne dissemination throughout the body**
- **May have many different presentations:**
 - **Acutely with fever, cough, night sweats, weight loss**
 - **Especially common in children and the HIV infected**
 - **Predominantly neurologic or other focal findings**
 - **FUO**
 - **Cryptic episodic symptoms - especially the elderly**

TB Radiographs



Tuberculosis



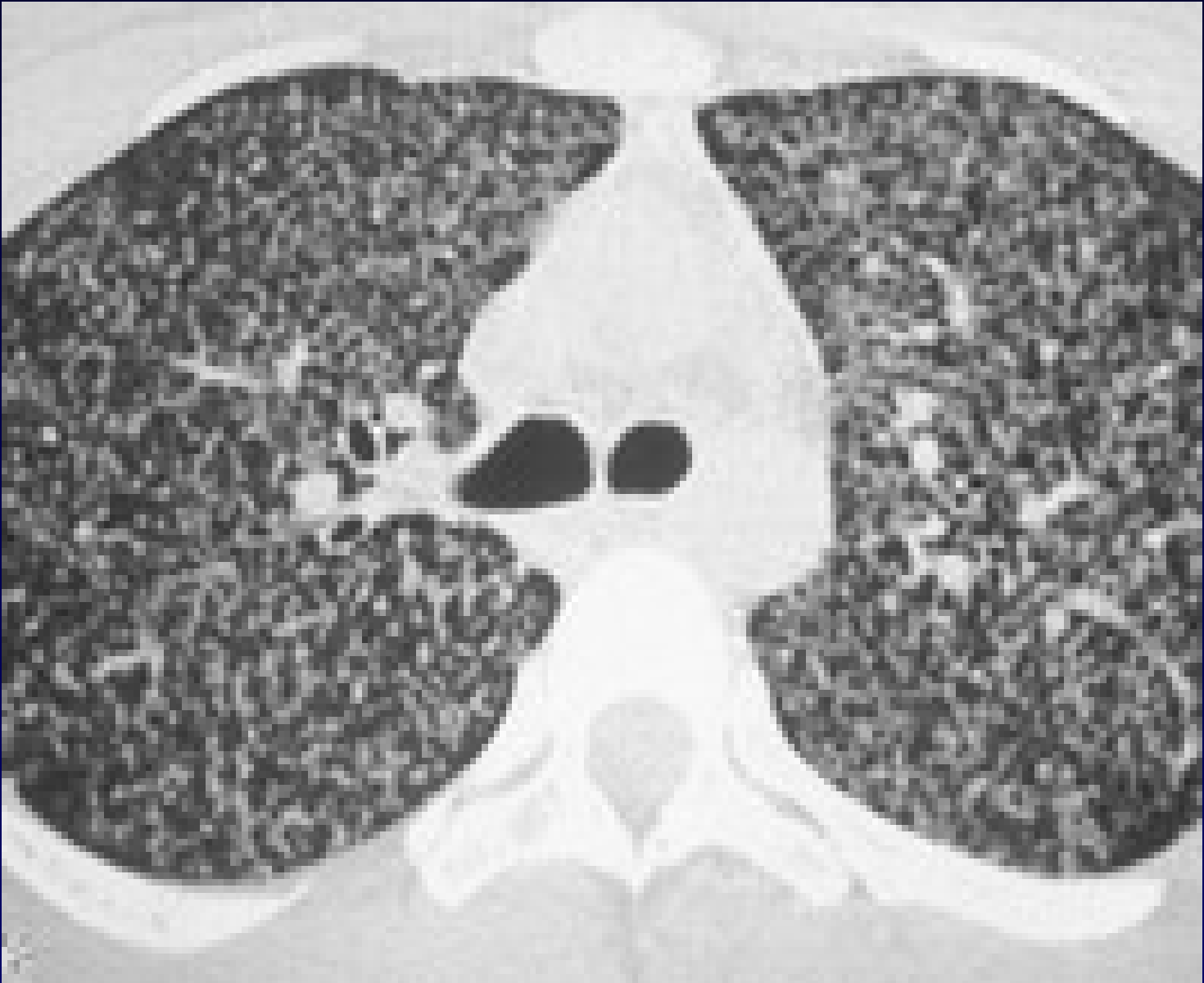
Fibroproliferative Disease



Miliary Disease



Miliary Disease



TB Diagnosis

Sputum Collection

- **TB suspects should have at least three sputum specimens examined by smear and culture.**
- **Methods:**
 - **Cough**
 - **Sputum induction**
 - **Gastric aspiration**
 - **Bronchoscopy**
 - **Biopsy**

TB Diagnosis - Sputum Collection

- TB suspects should have at least 3 specimens examined by smear and culture
 - Culture + confirms the diagnosis, but takes 3-6 weeks
- Follow-up microscopy/cultures are critical to evaluate response to therapy
- Sensitivity testing should be done on initial isolates, **in all cases**

Miliary/Extrapulmonary TB Diagnosis

- Aggressive diagnostic measures are needed.
- Smear and culture all available fluids
 - Smears are usually (-) and cultures may take weeks
- Tissue biopsies are frequently needed
 - Lung, lymph node, bone marrow, liver
- Get diagnostics performed ASAP and start rx



MMWRTM

Morbidity and Mortality Weekly Report

Recommendations and Reports

June 20, 2003 / Vol. 52 / No. RR-11

<http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf>

Treatment of Tuberculosis

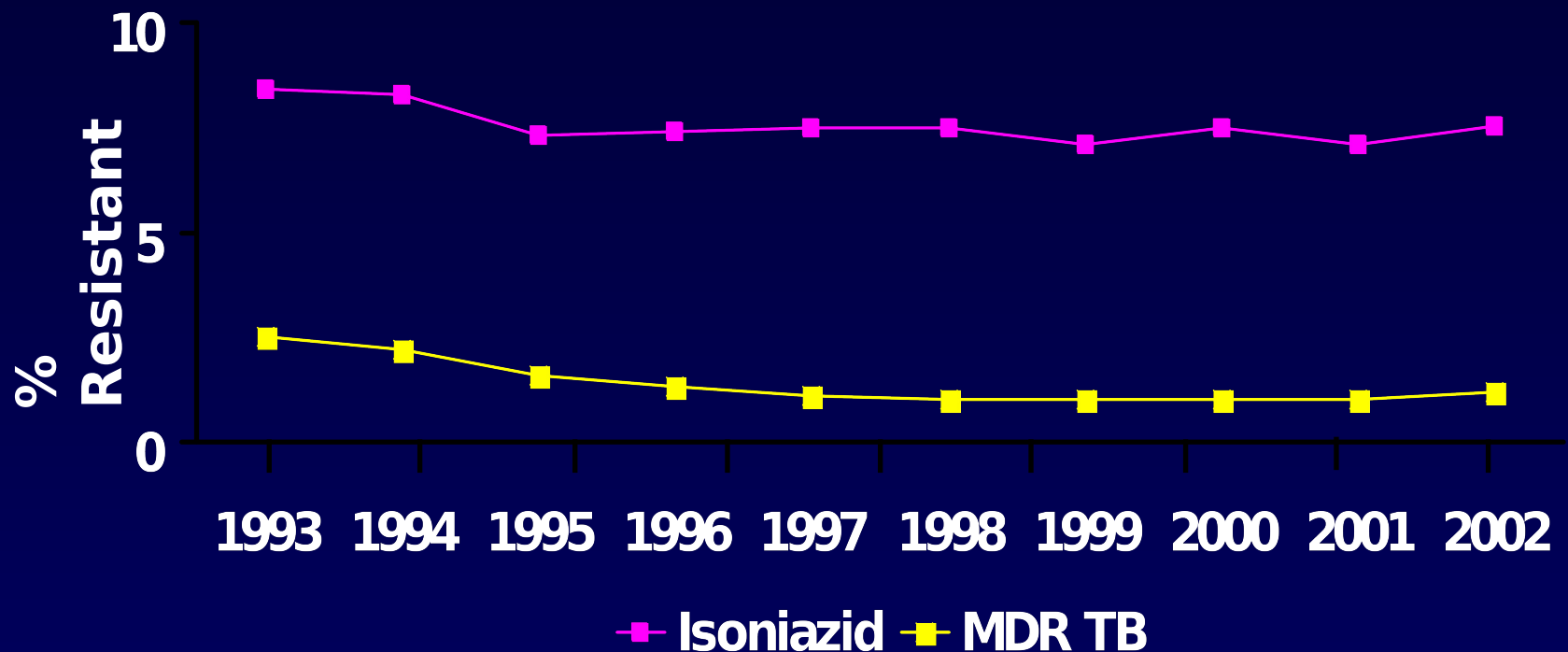
American Thoracic Society, CDC, and Infectious
Diseases Society of America

Basic Principles of Treatment

2003 CDC, ATS, IDSA Recommendations

- Provide safest, most effective therapy in the shortest time
- Initiate therapy with four drugs and always treat with at least two drugs
- Modify drugs to which the organisms are susceptible
- Never add a single drug to a failing regimen
- Nonadherence is a major problem
- Monitor at least monthly for adherence/adverse reactions

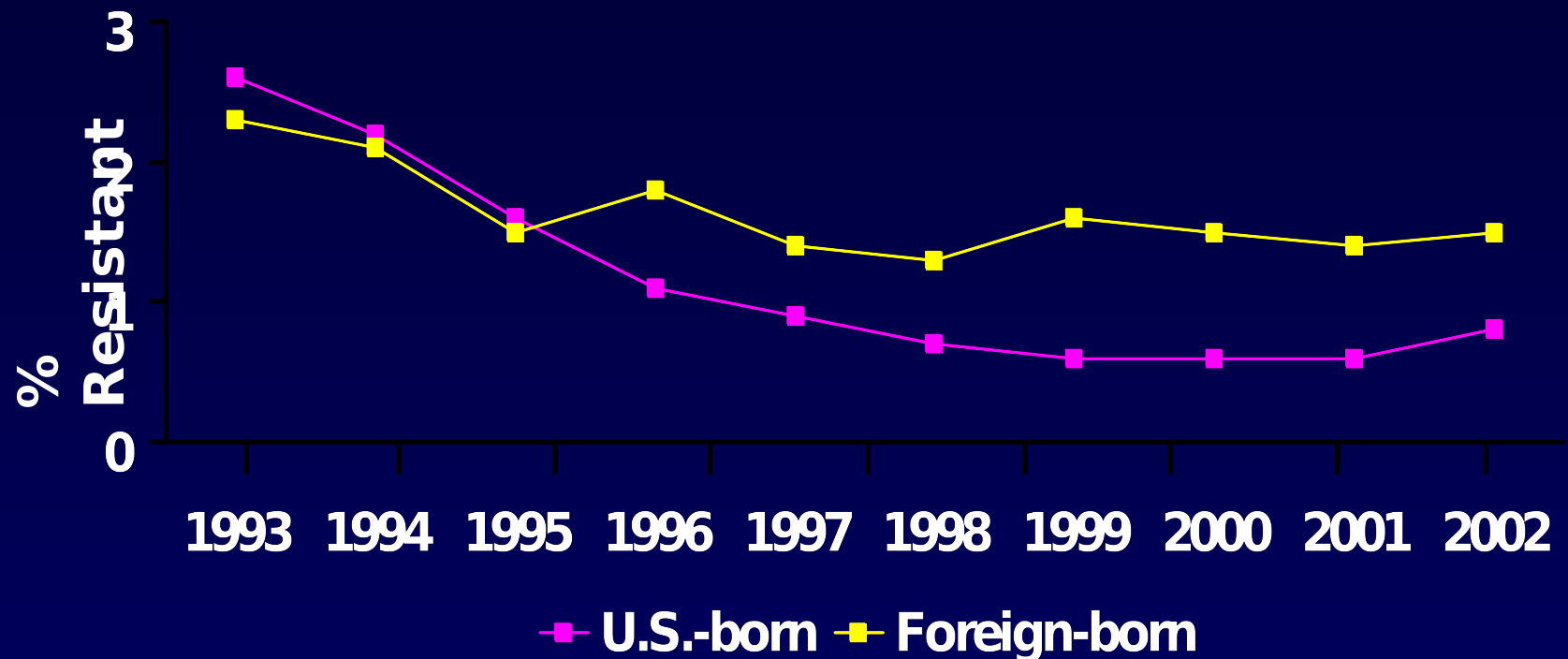
Primary Anti-TB Drug Resistance United States, 1993-2002



Note: Based on initial isolates from persons with no prior history of TB.

MDR TB defined as resistance to at least isoniazid and rifampin

Primary MDR TB in U.S.-born vs. Foreign-born, United States, 1993-2002



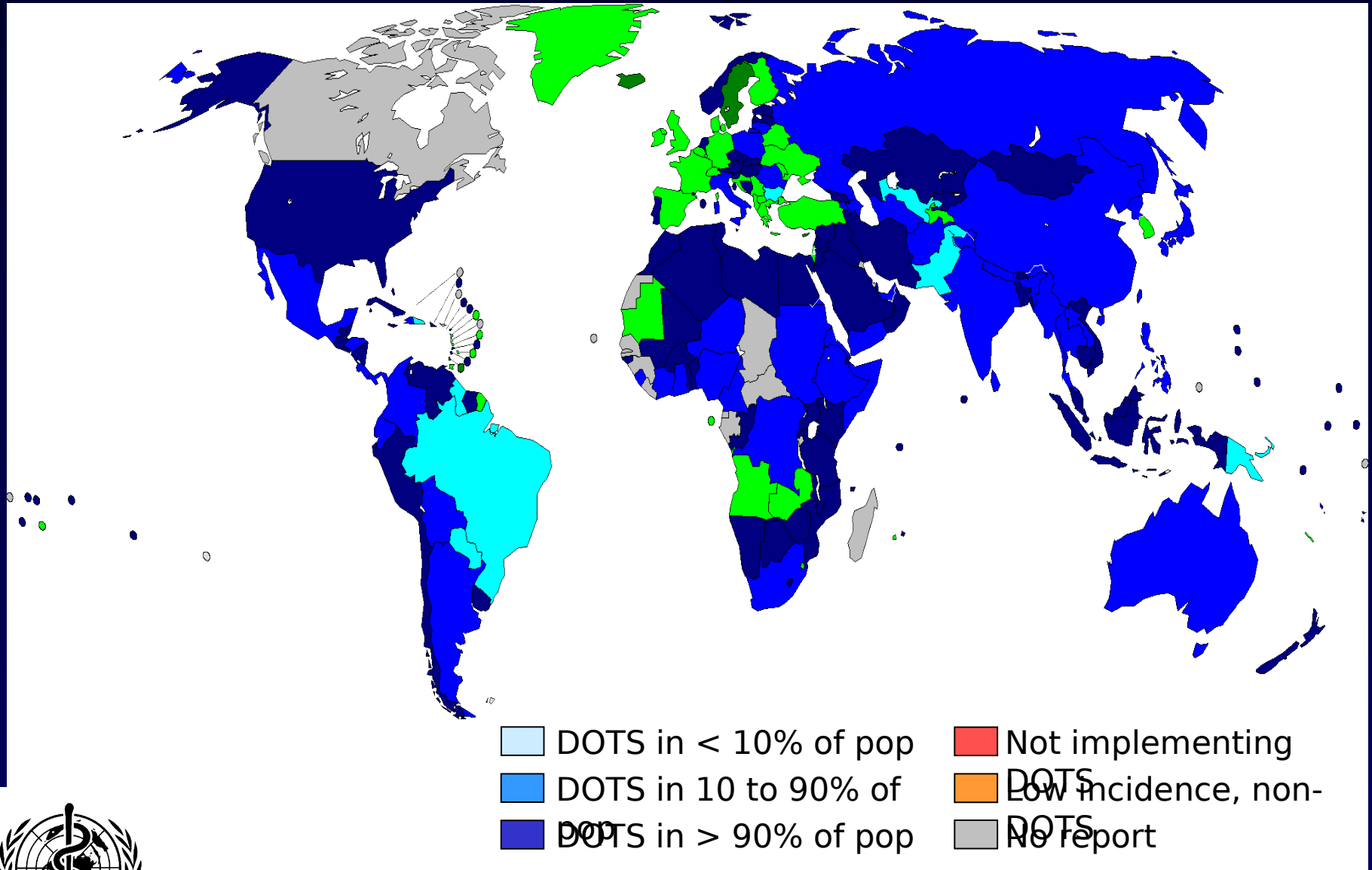
Note: Based on initial isolates from persons with no prior history of TB.

MDR TB defined as resistance to at least isoniazid and rifampin.

Directly Observed Therapy (DOT)

- Health care worker watches patient swallow each dose of medication
- Consider DOT for all patients
- Should be used with all intermittent regimens
- Use DOT with other measures to promote adherence
- Leads to reductions in relapse and acquired drug resistance

Implementation of DOTS, 2002



Antituberculosis Drugs

First-line drugs

- Isoniazid
- Rifampin
- Rifapentine
- Rifabutin*
- Ethambutol
- Pyrazinamide

Second-line drugs

- Cycloserine
- Ethionamide
- Levofloxacin*
- Moxifloxacin*
- Gatifloxacin*
- PAS
- Streptomycin
- Amikacin/kanamycin*
- Capreomycin

*Not approved by FDA for use in treatment of TB

TABLE 2. Drug regimens for culture-positive pulmonary tuberculosis caused by drug-susceptible organisms

Initial phase			Continuation phase			Range of total doses (minimal duration)	Rating* (evidence) [†]	
Regimen	Drugs	Interval and doses [‡] (minimal duration)	Regimen	Drugs	Interval and doses ^{‡§} (minimal duration)		HIV ⁻	HIV ⁺
1	INH RIF PZA EMB	Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk) [¶]	1a	INH/RIF	Seven days per week for 126 doses (18 wk) or 5 d/wk for 90 doses (18 wk) [¶]	182–130 (26 wk)	A (I)	A (II)
			1b	INH/RIF	Twice weekly for 36 doses (18 wk)	92–76 (26 wk)	A (I)	A (II) [#]
			1c ^{**}	INH/RPT	Once weekly for 18 doses (18 wk)	74–58 (26 wk)	B (I)	E (I)
2	INH RIF PZA EMB	Seven days per week for 14 doses (2 wk), then twice weekly for 12 doses (6 wk) or 5 d/wk for 10 doses (2 wk), [¶] then twice weekly for 12 doses (6 wk)	2a	INH/RIF	Twice weekly for 36 doses (18 wk)	62–58 (26 wk)	A (II)	B (II) [#]
			2b ^{**}	INH/RPT	Once weekly for 18 doses (18 wk)	44–40 (26 wk)	B (I)	E (I)
3	INH RIF PZA EMB	Three times weekly for 24 doses (8 wk)	3a	INH/RIF	Three times weekly for 54 doses (18 wk)	78 (26 wk)	B (I)	B (II)
4	INH RIF EMB	Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk) [¶]	4a	INH/RIF	Seven days per week for 217 doses (31 wk) or 5 d/wk for 155 doses (31 wk) [¶]	273–195 (39 wk)	C (I)	C (II)
			4b	INH/RIF	Twice weekly for 62 doses (31 wk)	118–102 (39 wk)	C (I)	C (II)

Definition of abbreviations: EMB = Ethambutol; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; RPT = rifapentine.

* Definitions of evidence ratings: A = preferred; B = acceptable alternative; C = offer when A and B cannot be given; E = should never be given.

[†] Definition of evidence ratings: I = randomized clinical trial; II = data from clinical trials that were not randomized or were conducted in other populations; III = expert opinion.

[‡] When DOT is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.

[§] Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31 week; either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.

[¶] Five-day-a-week administration is always given by DOT. Rating for 5 day/week regimens is AIII.

[#] Not recommended for HIV-infected patients with CD4⁺ cell counts <100 cells/μl.

^{**} Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on initial chest radiograph (see text). For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

TB Therapy - Children

- Same regimen as adults
- Ethambutol generally not used for children if visual acuity cannot be monitored
- TB in an infant is more likely to disseminate
 - Treatment should be started ASAP when suspected

TB Therapy - Pregnancy

- More aggressive in pregnancy so effective therapy is essential
- Preferred initial therapy is INH, rifampin, and ethambutol x 9 mo
 - Streptomycin may cause congenital deafness
 - Only licensed drug documented to have harmful effects on the fetus
 - Routine use of PZA is not recommended (risk of teratogenicity)
- Low levels of drugs in breast milk
 - does **not** preclude breast feeding during therapy
- PPD converter/reactor: If no disease, delay INH prophylaxis until post-partum

TB Therapy - Extrapulmonary Dz

- Same regimens/duration as pulmonary dz
- Some experts extended duration of therapy to nine to twelve months for:
 - Disseminated/Miliary disease
 - Bone and Joint disease
 - TB lymphadenitis
 - TB meningitis

TB - Screening Programs

Why?

- To identify TB-infected individuals who are at high risk of developing disease.
- To offer these individuals preventive therapy to minimize the risk of developing disease.

Tuberculosis

High-Risk Groups

- **HIV infected**
- **Close contacts of known infectious TB cases**
- **Persons with medical risk factors which increase the risk of TB **disease** in those TB **infected****
- **Foreign-born in areas of high prevalence**
- **Medically underserved low-income populations and minorities (Blacks, Hispanics, and Native Americans)**
- **Alcoholics and IV drug abusers**
- **Residents of jails, nursing homes, etc.**

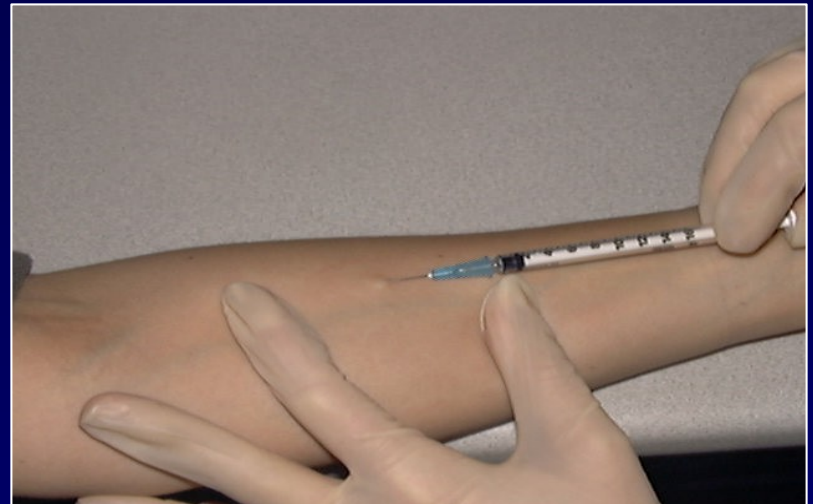
TB

Medical Conditions that Increase the Risk of a TB-infected Person Developing Tuberculosis

- HIV
- Silicosis
- Abnormal CXR with fibrotic lesions
- Diabetes
- Prolonged corticosteroids
- Immunosuppressive therapy
- Hematologic diseases (leukemia, Hodgkin's, etc.)
- End-stage renal disease
- Intestinal bypass
- Gastrectomy
- Chronic malabsorption
- Carcinoma of the oropharynx and UGI tract
- 10% or more below ideal body weight

TB - Tuberculin Skin Testing

- Target persons who would benefit from preventive therapy
 - Avoid screening low-risk populations
- Use intradermal Mantoux test
- 0.1 ml of 5 TU PPD tuberculin

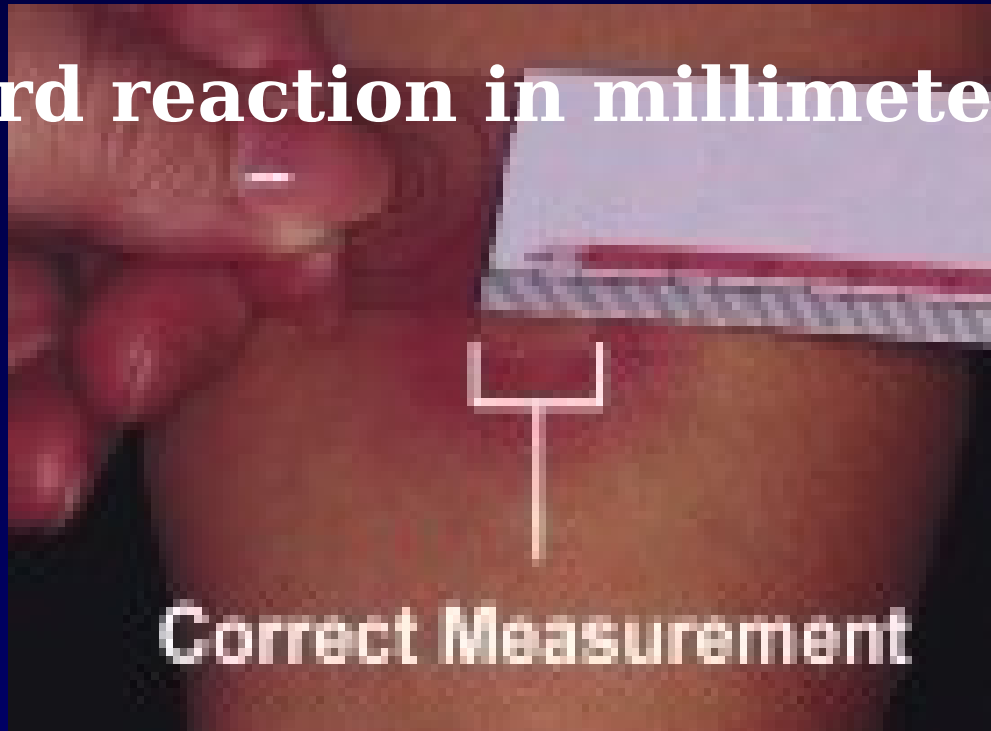


Tuberculin Skin Test

Read reaction 48-72 hours after injection

Measure only induration

Record reaction in millimeters



Limitations of Skin Test

- 20% of normal hosts with active TB do not react
- 30-80% of HIV+ persons with TB do not react
- **False-positive** Nontuberculous mycobacteria
BCG vaccination
- **False-negative** Anergy
Recent TB infection
Very young age (<6 mo)
Overwhelming TB disease

Anergy

- **Do not rule out TB diagnosis based on negative skin test result**
- **Consider anergy in persons with no reaction**
 - **HIV infected**
 - **Overwhelming TB disease**
 - **Severe or febrile illness**
 - **Viral infections**
 - **Live-virus vaccinations**
 - **Immunosuppressive therapy**
- **Anergy skin testing no longer routinely recommended**

Classification of Positive PPDs

Reaction of ≥ 5 mm induration is positive in:

- Close contacts of infectious cases
- HIV-infected patients
- Patients with CXR showing fibrotic lesions

Classification of Positive PPDs

Reaction of ≥ 10 mm induration is positive in:

- Patients with medical risk factors mentioned previously
- Foreign-born persons from high-prevalence areas
- Low-income populations, including high-risk minorities
- IV drug abusers

Classification of Positive PPDs

Reaction of ≥ 15 mm induration is positive in:

- Persons with no additional risk factors for TB
- Majority of Americans

The “Booster Phenomenon”

- **Some people with LTBI may have negative skin test reaction when tested years after infection**
- **Initial skin test may stimulate (boost) ability to react to tuberculin**
- **Positive reactions to subsequent tests may be misinterpreted as a new infection**

The “Booster Phenomenon”

Two-step testing

- If first test is (-), give second test a week later
- If second test is (+), classify as TB infected
- If second test is (-), classify as uninfected
- (+) on a third test (ie at annual screen) is likely to represent skin test conversion (ie a new infection)

Latent TB - Preventive Therapy

- Reduces an infected person's risk of developing clinical TB
 - 60% decrease in cases in most studies
- Monitor monthly for adherence and symptoms of toxicity

Tuberculosis

High Risk Groups to Target for INH Prophylaxis, Regardless of Age

- HIV Infected
- Close contacts of cases
- Recent skin test converters
 - > 10 mm increase for those < 35 yo
 - > 15 mm increase for those > 35 yo
- CXR with fibrotic lesions
- IV drug abusers
- Other medical conditions that increase risk of TB

Tuberculosis

High Risk Groups to Target for INH Prophylaxis, for Persons < 35 yo

- Foreign-born from high prevalence areas
- Low-income populations, including high-risk minorities
- Jail, nursing home residents, barracks, ships, etc.

LTBI Treatment Options

- Isoniazid daily or biweekly for 9 months
- Rifampin daily for 4 months
- (PZA + Rifampin daily for 2 months)
- CAUTION: Fatal or severe liver toxicity may occur, especially with PZA/Rif
 - Choose patients carefully and follow LAEs

TB - Drug Toxicity

Caution patients to be aware of and report certain symptoms:

- Loss of appetite
- Vomiting
- Jaundice
- Unexplained fever
- Nausea
- Dark urine
- Malaise
- Abdominal pain

TB - Isoniazid

Before starting patients on therapy:

- Examine for signs of liver disease or neuropathy
- Discuss alcohol use
- Give warning signs of hepatitis
- Get a baseline liver-associated enzymes and bilirubin
- Counsel patient on why you are doing this

Isoniazid - Precautions

- Age > 35 years old
- Taking other medications on a long-term basis
- Alcohol abusers
- History of previous discontinuation of therapy
- Chronic liver disease
- Peripheral neuropathy
- Pregnancy

INH Toxicity

- Estimated risk of hepatitis 20.7 per 1,000 treated??
- 4.6% of those who develop INH-associated hepatitis die
- Risk of hepatitis approximately 3x higher if > 35 yo
- 69% of patients with fatal hepatitis are female.
- No specific diagnostic criteria or pathological findings, i.e. diagnosis of exclusion

MMWR 1993;42:545-547

TB - BCG

- Numerous meta-analyses of studies have shown that BCG vaccination definitely decreases the number of cases of TB meningitis in children and, to a lesser extent, pulmonary TB, in areas of high prevalence
- BCG vaccination is currently recommended for children, though not in the U.S.
- Not recommended in the U.S. due to the low prevalence of TB, lack of efficacy in U.S. studies, and the desire to keep PPD skin testing a useful tool

TB

Skin Testing and BCG

- Positive PPD in a patient with a history of BCG usually indicates infection with *M. tuberculosis*.
- Initial PPD positivity wanes within a few years of receiving BCG vaccination.

TB - Infection Control

- Chemotherapy of source case
- Patient hygiene
 - Cover mouth/nose when coughing, laughing, sneezing
- Adequate ventilation
 - Six exchanges of room air per hour
- Ultraviolet lights

TB - Infection Control

- Precautions to prevent transmission are especially important during:
 - Sputum collection/induction
 - Bronchoscopy
 - Pentamidine nebulizations
- Procedures should be performed in rooms with adequate ventilation.

TB - Infection Control

HIV-infected patients:

- All patients with HIV and undiagnosed pulmonary disease should be considered TB suspects
- Patients should be isolated until sputum x3 has been shown to be smear negative or adequate therapy has been begun.

Tuberculosis

Factors Influencing Transmission

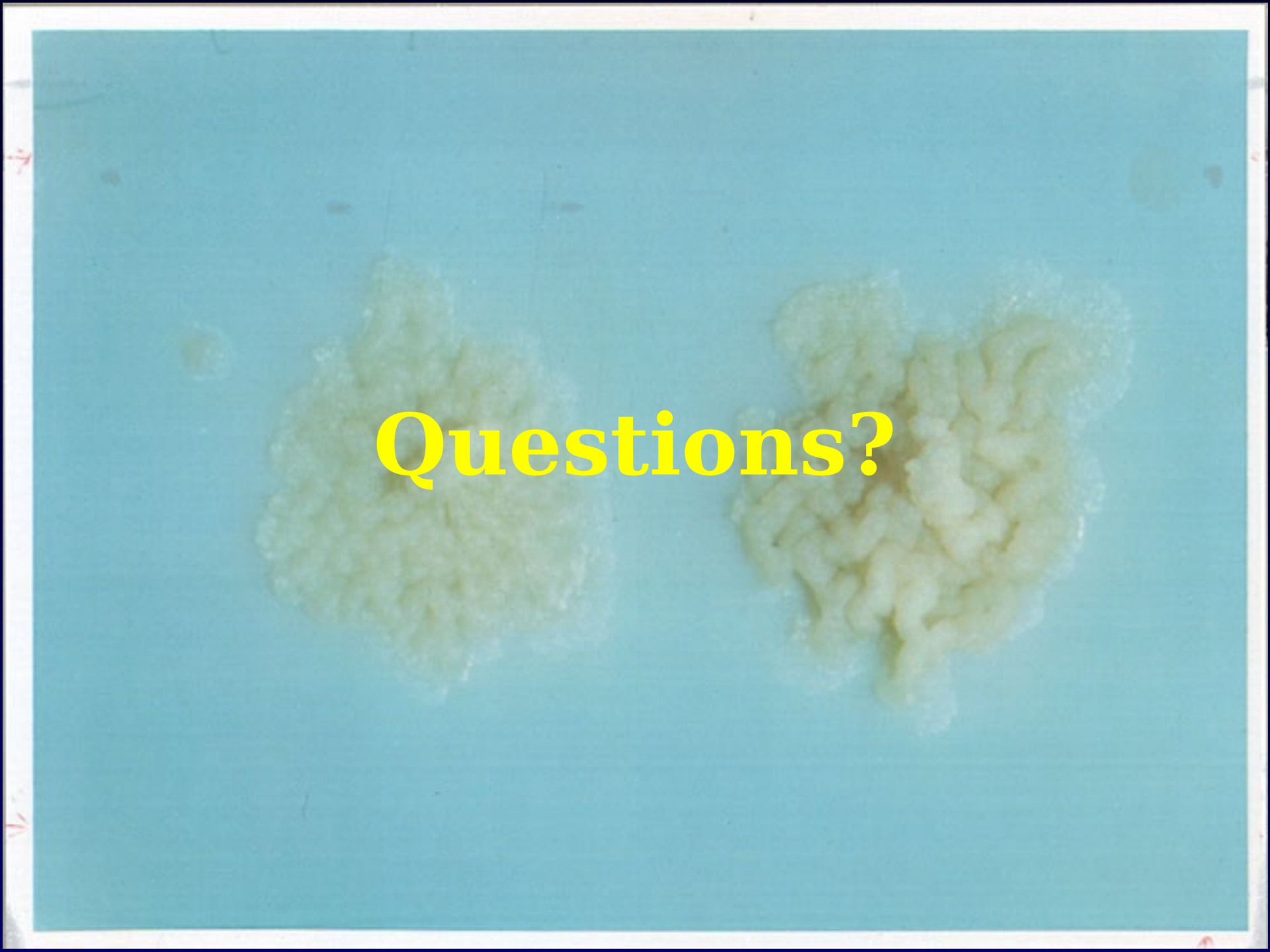


Tuberculosis

USS Wasp (LHD-1) med cruise Feb to July 1998

- Marine dx with active pulmonary TB med-evaced in May
- 270 sailors and Marines screened as “close contacts”
 - 27 converters (10% conversion rate) and 1 case
- 2043/2138 (95.6%) of MEU screened
 - 114 not tested, 53 prior reactors, 42 converted from May
 - 469/2085 (22.5%) converters with additional 56 converters at 3 month testing, 525/2085 (25.2%) total converted
 - 56 converters had abnl CXRs and had sputa examined
 - 14/56 had active TB (9 pulmonary and 5 pleural)
- 1019 USS Wasp crew tested in August:
 - original screening- 132 converters, 85 previous reactors and 3 cases
 - 3 month f/u - 39 more converters
 - 13/262 riders (Midshipmen, etc.) also converted
 - Final tally 18.3% of crew converted

LeMar, Sposato, et al. Navy and Marine Corps Team TB Outbreak NMSR Apr-Jun '99; 6-11.

The image shows two distinct, yellowish, clumpy masses on a light blue background. The mass on the left is more rounded and compact, while the mass on the right is more elongated and irregular. Both masses have a granular, almost crystalline texture. The word "Questions?" is superimposed in the center in a bold, yellow, serif font.

Questions?